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Motor palsies of cranial nerves (excluding VII) after vaccination

Reports to the US Vaccine Adverse Event Reporting System

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We reviewed cranial nerve palsies, other than VII, that have been reported to the US Vaccine Adverse Event Reporting System (VAERS). We examined patterns for differences in vaccine types, seriousness, age, and clinical characteristics. We identified 68 reports of cranial nerve palsies, most commonly involving the oculomotor (III), trochlear (IV), and abducens (VI) nerves. Isolated cranial nerve palsies, as well as palsies occurring as part of a broader clinical entity, were reported. Forty reports (59%) were classified as serious, suggesting that a cranial nerve palsy may sometimes be the harbinger of a broader and more ominous clinical entity, such as a stroke or encephalomyelitis. There was no conspicuous clustering of live vs. inactivated vaccines. The patient age range spanned the spectrum from infants to the elderly. Independent data may help to clarify whether, when, and to what extent the rates of cranial nerve palsies following particular vaccines may exceed background levels.

Introduction

Bell's palsy has been reported following seasonal influenza vaccine,[1-3] H1N1 influenza vaccine,[4] hepatitis B vaccine,[5] and smallpox vaccine,[6] but a causal relationship has not been established. A possible association of facial nerve palsy and influenza vaccination has been reported.[7,8] Mutsch et al.[8] found a statistically significant association of Bell's palsy following an inactivated intranasal influenza vaccine used in Switzerland. The heat-labile *Escherichia coli* enterotoxin used as an adjuvant in that vaccine was suspected[9] to play a role, and Lewis et al.[10] later demonstrated a plausible biological pathway by which the adjuvant (no longer used in licensed human vaccines) could result in facial nerve palsies. However, Stowe et al.[11] performed a self-controlled case-series analysis and found no increase in the risk of Bell's palsy in the three months after inactivated influenza vaccine. Similarly, Lee et al.[12] conducted a case-centered analysis and reported no association of Bell's palsy with monovalent influenza H1N1 vaccine nor trivalent inactivated influenza vaccine.

The Institute of Medicine's Committee to Review Adverse Effects of Vaccines[13] concluded that the evidence favors rejection of a causal relationship of inactivated influenza vaccine and Bell's palsy, but we are not aware of any formal, large-scale evaluations of a possible causal association of other cranial nerve palsies and vaccination. Williams et al.[14] assessed the causality of adverse events following influenza H1N1 vaccination. Their review[14] included a single case of cranial VI palsy 13 d after influenza H1N1 vaccine and trivalent seasonal influenza vaccine, in a 15-y-old male who also had a history of headaches and sports-related concussions. Based on the time course and concomitant exposures, the authors[14] concluded that cranial neuropathy—including Bell's palsy and optic neuritis, as well as the case of abducens palsy—had a "possible" causal relationship with vaccination, according to modified World Health Organization criteria.

The purpose of this analysis is to describe cranial nerve palsies, other than VII, that have been reported to the Vaccine Adverse Event Reporting System (VAERS) after routine vaccination. Because motor deficits may be more concerning to patients and clinicians than purely sensory neuropathies, and because sensory changes are highly subjective and difficult to document, this analysis focuses on palsies. Therefore disturbances of cranial nerve VIII and the sensory branches of V are not included.

Results

We identified 108 reports of possible cranial nerve palsies. Upon manual review, 37 reports were found to contain no symptoms of cranial nerve paresis or paralysis; often these reports described sensory disturbances of cranial nerves (e.g., trigeminal neuralgia or hypoacusis) with no motor deficit, one report was determined to be a duplicate of an earlier report, and two reports were excluded because they concerned cranial nerve palsies that

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Table 1. Demographics of cranial nerve palsy cases

	Single vaccine	Multiple vaccines	Total
	n = 43	n = 25	n = 68
Age (years)			
<2	3	10	13
2–17	12	10	22
18–64	17	4	21
≥65	10	1	11
Unknown	1	0	1
Sex			
Female	22	13	35
Male	20	12	32
Unknown	1	0	1
Serious[15]	24	16	40
Non-serious	19	9	28
Onset* of cranial nerve palsy (days)			
n	40	25	65
Median	9	10	9
Range	0.3–3285	0.23–474	0.23–3285

*For 3 reports, onset information was not provided.

began before vaccination. Thus, 68 reports remained in the analysis, with 43 listing a single vaccine and 25 listing multiple concomitantly administered vaccines. Demographic information is summarized in **Table 1**. There were no conspicuous patterns relating to age or sex, and 40 cases (59%) were classified as serious.[15] There were no reports of positive rechallenge (i.e., recurrent cranial nerve palsy after subsequent doses of the same vaccine), nor any elevated values for disproportionality.[16]

The most commonly involved cranial nerves were oculomotor, trochlear, and abducens (**Table 2**). In 48 cases (71%), the cranial nerve palsy was the primary adverse event reported to VAERS. For example, a 1-y-old girl developed disconjugate gaze six days after routine immunization with live measles, mumps, and rubella vaccine. There was no documentation of an alternative explanation, such as a head injury or recent illness. The patient was admitted to the hospital for a diagnostic work-up of new-onset left cranial nerve VI palsy. Investigations included magnetic resonance imaging and CT of the brain, complete blood count, comprehensive metabolic profile, and blood cultures. All tests were within normal limits, and Guillain-Barré Syndrome was ruled out. The discharge diagnoses included idiopathic abducens nerve palsy on the left and disconjugate gaze.

In many cases that were classified as serious, the cranial nerve palsy occurred as part of a broader clinical entity, such as acute disseminated encephalomyelitis, cerebrovascular accident, diabetes mellitus, multiple sclerosis, meningitis, intracranial hypertension, or cancer of the central nervous system. For instance, a 71-y-old man with pre-existing symptoms of an upper respiratory infection developed fever, malaise, and anorexia two days after influenza H1N1 vaccination. He was hospitalized twice and received supportive care. Discharge diagnoses included elevated liver function tests, possibly secondary to a viral infection; mesenteric panniculitis; elevated hemoglobin A1C; and fatty infiltration of the liver. Twenty-four days after vaccination, he developed diplopia. He was evaluated as an outpatient and was diagnosed with diabetic third nerve palsy, which reportedly resolved.

Cranial nerve palsies were reported after a wide variety of vaccines (**Table 3**). Most reports (43; 63%) listed a single vaccine. Among reports listing single vaccines, the most common vaccines were influenza vaccine seasonal trivalent inactivated, human papillomavirus vaccine quadrivalent, influenza H1N1 vaccine inactivated, and zoster vaccine live. Among reports listing multiple vaccines, the most common vaccines included hepatitis A vaccine; measles, mumps, and rubella vaccine live; diphtheria and tetanus toxoids and acellular pertussis vaccine; Hemophilus influenzae type b vaccine; and pneumococcal conjugate vaccine 7-valent. There was no conspicuous clustering of live or inactivated vaccines with palsies of particular cranial nerves.

Discussion

To our knowledge, this is the first review of palsies of cranial nerves, other than VII, after routine immunization. Palsies of

Table 2. Cranial nerve palsies (other than VII) reported to VAERS

Cranial nerve*	Isolated cranial nerve palsy	Cranial nerve palsy as component of broader clinical entity	Total
III Oculomotor	13	9	22
IV Trochlear	6	3	9
VI Abducens	27	5	32
IX Glossopharyngeal	0	2	2
X Vagus	1	1	2
XII Hypoglossal	0	2	2
Not Specified**	2	1	3

*There were three reports of multiple cranial nerve palsies: nerves IX + X + XII (1 report), nerves III + IV (1 report), and nerves III + VI (1 report). **Reported as "cranial nerve paralysis" without further details.

Table 3. Vaccines most commonly listed on reports of cranial nerve palsies

Vaccines[1]	Reports
Influenza vaccine, seasonal trivalent inactivated	14
Hemophilus influenzae type b vaccine	8
Human papillomavirus vaccine quadrivalent	7
Measles, mumps, and rubella vaccine live	7
Pneumococcal conjugate vaccine 7-valent	7
Diphtheria and tetanus toxoids and acellular pertussis vaccine	6
Hepatitis A vaccine	6
Hepatitis B vaccine	6
Influenza vaccine, H1N1 inactivated	6
Diphtheria and tetanus toxoids and acellular pertussis, Hemophilus influenzae type b, and inactivated poliovirus vaccine	5
Poliovirus vaccine inactivated	5
Zoster vaccine live	5
Varicella vaccine live	4
Influenza vaccine, seasonal trivalent live intranasal	3
Meningococcal (A, C, Y and W-135) conjugate vaccine	3
Pneumococcal conjugate vaccine 13-valent	3
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine	3
Other	20

[1]Vaccines are not mutually exclusive. Therefore, the sum of the counts exceeds the total number of reports.

cranial nerves III, IV, and VI were the most commonly reported deficits in this analysis, but other cranial nerves were also affected. Like Bell's palsy, the symptoms associated with ptosis, gaze deviation, and other cranial nerve palsies can be distressing for the patient and puzzling for the clinician. In particular, insufficiencies of visual convergence or accommodation may impair the ability to read, drive, and perform other important activities of daily living. More than half of cranial nerve palsies in our study were reported as serious,[15] suggesting that a cranial nerve palsy may sometimes be the harbinger of a broader and more ominous clinical entity, such as a stroke or encephalomyelitis. It seems plausible that serious cases are more likely to be reported than non-serious ones,[17,18] and there could be substantial underreporting of cases that are managed on an outpatient basis.

Cranial nerve palsies have been reported to VAERS following a wide variety of inactivated and live attenuated vaccines. Reports for trivalent inactivated influenza vaccine were the most frequent among single-vaccine reports, but they constituted only a weak plurality and not an overwhelming majority. The reports listing multiple vaccines largely reflected the most common combinations of routine immunizations administered to infants and young children: Diphtheria and tetanus toxoids and acellular pertussis vaccine, Hemophilus influenzae type b vaccine, Pneumococcal conjugate vaccine 7-valent, and Poliovirus vaccine inactivated given together, as well as measles, mumps, and rubella vaccine live co-administered with varicella vaccine live. Passive surveillance data cannot be used to assess causality; the occurrence of cranial nerve palsies after vaccination may be purely coincidental.

Strengths of VAERS include its national scope, size (more than 30 000 reports per year in recent years), timeliness, ability to detect events that were not observed during prelicensure trials, and surveillance among special populations, such as travelers and military personnel.[19] However, passive surveillance systems such as VAERS are subject to many limitations, including underreporting, incomplete information in many reports, inadequate data regarding the number of doses administered, and lack of a direct and unbiased comparison group.[20-22] Because of these and other limitations, it is not possible to determine causal associations between vaccines and adverse events based on VAERS reports. Nevertheless, VAERS data can be used to identify rare events that might not have been observed during prelicensure trials, and to look for unexpected patterns in demographics and clinical characteristics that might lead to hypotheses that could be tested with controlled, epidemiological methods.

Because of inconsistent report quality, there was great variability in the information provided about concomitant exposures (e.g., medications), medical history (e.g., infections or vasculopathy), symptom onset interval, and accompanying symptoms. Medical records were not always available to allow assessment of alternative etiologies of a patient's cranial nerve palsy. The relatively small number of cases in this series and the heterogeneity of vaccines listed on these reports limit our ability to draw any definitive conclusions about a possible causal relationship with cranial nerve palsies. The lack of an unvaccinated control group prevents calculation of relative risks. Distinguishing causality from coincidence is notoriously difficult, particularly for events with low background incidence, i.e., those that are rare even in the unexposed population. Independent data may help

to identify patterns and clarify whether the rates of cranial nerve palsies following vaccination exceed background levels[23] or differ qualitatively from cases resulting from congenital conditions, trauma, or other causes.[24] FDA's Mini-Sentinel System[25] and the Vaccine Safety Datalink[26] may provide an opportunity to evaluate and characterize a possible relationship of cranial nerve palsies and routine vaccinations, and the Clinical Immunization Safety Assessment network[27] might help to elucidate whether a plausible biological mechanism exists. Post-immunization cranial nerve palsies other than VII may be clinically important, and further research is needed.

Materials and Methods

VAERS

Established in 1990 in accordance with the National Childhood Vaccine Injury Act of 1986, VAERS is jointly managed by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention.[19] These spontaneous reports of suspected vaccine side effects are submitted by health care providers, vaccine recipients, vaccine manufacturers, and other interested parties.[19] Federal regulations require manufacturers to report all adverse events occurring within the US, and all serious and unexpected adverse events occurring outside the US.[15,19] Healthcare professionals and consumers are encouraged to report adverse events[19]; individuals may report an adverse event even if they are not certain that the vaccine caused it. FDA medical officers review all serious adverse events, which for regulatory purposes are defined as those reported as fatal, disabling, life-threatening, requiring hospital admission, prolonging a hospital stay, resulting in a congenital anomaly, or requiring medical intervention to prevent such an outcome.[15] VAERS data may be used to detect new or rare adverse events, monitor known reactions, perform vaccine lot surveillance, identify risk factors, and evaluate the safety of newly licensed vaccines.[19]

Report identification and review

We selected all VAERS reports (July 1, 1990–January 30, 2012) with any of the following Medical Dictionary for Regulatory Activities (MedDRA Version 13.1) Preferred Terms (PTs): IIIrd nerve disorder, IIIrd nerve paralysis, IIIrd nerve paresis, IVth nerve disorder, IVth nerve paralysis, IVth nerve paresis, trigeminal nerve disorder, trigeminal palsy, trigeminal nerve paresis, VIth nerve disorder, VIth nerve paralysis, glossopharyngeal nerve disorder, glossopharyngeal nerve paralysis, vagus nerve disorder, vagus nerve paralysis, accessory nerve disorder, XIth nerve paralysis, hypoglossal nerve disorder, hypoglossal nerve paralysis, hypoglossal nerve paresis, cranial nerve disorder, cranial nerve injury, cranial nerve palsies multiple, cranial nerve paralysis, cranial neuropathy, or paresis cranial nerve. We reviewed the reports to identify the involved cranial nerve(s) and verify that the adverse event included paresis or paralysis. We summarized the results with descriptive statistics.

Disproportionality analysis

Data mining methods can identify adverse events that are reported more commonly for one vaccine than others. Disproportionally high reporting of a given event after a specific vaccine does not imply a causal relationship, but may indicate that further investigation is warranted. We applied Empirical Bayesian methods[16] to identify disproportionality in reporting of the aforementioned MedDRA PTs, covering the same time period, in order to identify vaccine-event pairs that deserved further review.

Disclosure of Potential Conflicts of Interest

The authors have no conflicts of interest. The current study was conducted as part of routine public health surveillance, and there was no funding source.

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